

# *Research Progress on the Pharmacological Mechanism of Sour Date Palm in the Treatment of Insomnia with Anxiety and Depression*

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**Keywords:** Sour date palm, insomnia with anxiety and depression, saponins, pharmacological mechanism, flavonoids

**Abstract:** Insomnia with anxiety and depression is one of the common psychological disorders, which are closely related and usually appear in the form of co-morbidity. The pathogenesis of this disease is still unclear, but it is mostly related to the function of the hypothalamic-pituitary-adrenal axis (HPA axis), neurotransmitter regulation, and inflammatory response. According to Chinese medicine, this disease belongs to the category of "sleeplessness", "depression" and "dirty restlessness", involving the five internal organs and six internal organs. Modern pharmacological studies have shown that sour date kernel contains flavonoids, saponins, triterpenoids, and phenolic acid compounds. It is also found to act simultaneously through sedative-hypnotic, anti-anxiety, anti-depressant, neurotransmitter regulation, inflammation inhibition, and brain nerve protection. In this paper, the pharmacological effects and mechanisms of the active ingredients of *Ziziphus jujube* were described by reviewing the pharmacological research literature related to *Ziziphus jujube*, to illustrate the positive efficacy and medicinal value of *Ziziphus jujube* in the treatment of insomnia with anxiety and depression.

## 1. Introduction

### 1.1. Brief description of insomnia with anxiety and depression

Insomnia is a common sleep disorder category, long-term insomnia is prone to mood disorders, with anxiety and depression as the main manifestations [1]. Insomnia has a complex bidirectional relationship with anxiety and depression, and they influence each other, and insomnia is an indispensable criterion in the diagnosis of depression, and at the same time, insomnia can greatly increase the prevalence of some neuropsychiatric disorders. According to statistics, about 90% of patients suffering from depression have symptoms of insomnia [2], and insomnia patients with varying degrees of depression and anxiety account for 5%-30% of the total number of patients [3], which can easily lead to more serious physical and psychological diseases if not treated promptly, and seriously affect people's daily quality of life and physical and mental health.

The biological mechanisms underlying the pathogenesis of the disease are currently unknown and are mostly associated with hypothalamic-pituitary-adrenal axis (HPA axis) function, neurotransmitter mechanisms, inflammatory responses, and active cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 (IL-1) [4,5]. Clinical medicine mostly treats this disease with a combination of sedative and antidepressant drugs, which have a lot of side effects and poor results in the long term. Traditional medicine in China considers insomnia with anxiety and depression to be a combination of "sleeplessness" and "depression", involving the five viscera and six internal organs. The pathogenesis is always "qi imbalance, yin, and yang, imbalance of the internal organs". In ancient times, the major medical scholars have a different understanding of this disease, but most of them mixed deficiency and reality, the deficiency is mostly Yin deficiency and fire, the reality is mostly liver depression and fire, and the nature of the pathology is real at the beginning, but it is a deficiency or mixed with deficiency and reality.

## 1.2. Introduction of Sour Date Palm

The use of sour date kernel, which can nourish the heart and nourish the liver and calm the mind, was found to be extremely frequent through a study of the usage patterns of prescription drugs for insomnia anxiety, and depression in ancient and modern literature. In this paper, we investigate the pathogenesis of insomnia with anxiety and depression and the pharmacological effects of sour date kernel and make a review and analysis of the mechanism of sour date kernel in the treatment of insomnia with anxiety and depression.

## 2. Overview of research on sour date palm

Sour jujube kernel, also known as jujube, is the dried mature seeds of *Ziziphus jujuba* Mill. var. *Spinosa* (Bunge) Hu ex H. F. Chou, a plant in the family Rhamnaceae, mainly from Shaanxi and Hebei [6]. In the Compendium of Materia Medica, it is suggested that *Ziziphus jujube* "is used for the treatment of deficiency sweat and thirst, and sleeplessness, and can be taken for a long time to calm the five organs", and can be used as a long-term medicine for chronic insomnia [7,8]. Modern masters of Chinese medicine believe that sour date kernel has various effects in the treatment of insomnia anxiety and depression, and Zhou Zhongying and Zhang Lei et al. believe that fried sour date kernel can clear heat and remove annoyance, nourish the heart and tranquilize the mind, nourish blood and soften the liver, and is effective in treating insomnia with yin deficiency and fire with dirty agitation and depression [9,10].

Modern pharmacological studies have shown that sour date kernel contains flavonoids, saponins and triterpenoids, alkaloids, fatty oils, and other chemical components [11]. Existing research results also indicate that sour date kernel has sedative-hypnotic, anxiolytic, antidepressant, mild vasodilator, hepatoprotective, antioxidant, and memory-improving pharmacological effects, which can act together in multiple targets and aspects. For example, the flavonoid spinosin in date palm can reduce the NE and 5-HT content in the hippocampus and decrease the  $\beta$ -endorphin content to achieve anxiolytic effects, which is widely used in the treatment of insomnia, anxiety, depression, and other neurological disorders. Depression, and other neurological disorders [12]. At present, there are relatively few studies on the active ingredients and mechanisms of action of sour date kernel, etc. In this paper, we describe the mechanisms related to insomnia with anxiety and depression and the pharmacological effects and components of sour date kernel to explore its pharmacological mechanisms.

### 3. Therapeutic mechanism of sour date palm in insomnia with anxiety and depression

#### 3.1. Regulation of hypothalamic-pituitary-adrenal (HPA) axis function

When the body is under stress for a longer period, adrenocorticotropin-releasing hormone (CRH) causes a hormonal cascade response along the HPA axis and projects directly to the limbic system to regulate stress behavior [13]. At this time, the HPA axis is hyper-functional, forcing the anterior pituitary to produce adrenocorticotrophic hormone (ACTH), which allows the activation of a large number of inflammatory factors that exert sleep-promoting and inhibiting effects, respectively [14]. It also affects the synthesis and metabolism of  $\gamma$ -aminobutyric acid (GABA) [15]. On the one hand, GABA is an inhibitory neurotransmitter, and glutamate (GLU) is an excitatory neurotransmitter, and an imbalance in the ratio of the two can lead to neuronal degeneration and necrosis, forming damage to hippocampal neurons, hypothalamus, and amygdala, and aggravating depression [16]. On the other hand, serum levels of GABA and brain-derived neurotrophic factor (BDNF), a molecule related to synaptic plasticity, are positively correlated, and impairment of synaptic plasticity can be caused by a decrease in central BDNF levels, and reduced neuroplasticity can cause hippocampal, hypothalamic, and amygdala damage and aggravate depression [17]. Traditional medicine in China considers sour date palms to have significant efficacy in the treatment of insomnia anxiety and depression, and it is one of the few herbs used more frequently. One of the main active ingredients in sour date palms is flavonoids, which are mostly flavonoid carbohydrates. It was found that sour date brassica had significant sedative-hypnotic effects and increased the duration of sodium barbiturate-mediated sleep [18]. The expression of GABA receptor subunits in hippocampal neurons of rats treated with dangiferulose brassicas was enhanced, and diazepam treatment also resulted in altered expression of GABAA  $\alpha$ 1 and others, indicating that the sedative effect of dangiferulose brassicas may be similar to that of diazepam [19].

The sour date palm combination is more often used in clinical practice for the treatment of insomnia with anxiety and depression. The research results of Wang Yue et al. showed that sour date palm soup could increase BDNF protein expression and help improve sleep-induced anxiety-like behavior in rats [20]. In a study on Tianwang Tonic Heart Dan, Zhao Qian et al. confirmed that total saponin of sour date palm could alter the content of Glu and GABA neurotransmitters and receptors in the cortex and hippocampus of aged insomniac rats, resulting in increased slow-wave sleep [21]. In conclusion, Ziziphi jujube can significantly improve the symptoms of insomnia in anxiety and depression patients by modulating neurotransmitters.

#### 3.2. Regulation of neurotransmitters

It is believed that the secretion of the monoamine neurotransmitter 5-hydroxytryptamine (5-HT) is closely related to the development of insomnia with anxiety and depression. 5-HT induces sleep in the brain by enhancing the secretion and accumulation of peptides with hypnotic effects in the hypothalamus and acting synergistically with neurotransmitters such as NE and dopamine (DA) [22].

The main active components of date palms that affect sleep are flavonoids and saponins and alkaloids. The material basis of the anxiolytic effect of the date palm is flavonoids, and spinoside is one of the flavonoids that can shorten sleep latency, increase total sleep time, and exert its sedative-hypnotic effects through 5-hydroxytryptamine (5-HT). Date palm saponin components can shorten sleep latency in mice, where spontaneous activity can be significantly reduced by date palm saponin A and date palm saponin B. Yoon et al. showed that oral administration of date palm saponin A alleviated and protected against hippocampal neuronal damage and apoptosis induced by erythropoietin (KA) [23]. Meanwhile, there is no significant drug dependence in the treatment of

patients with long-term insomnia using date palm saponin A. Therefore, date palm saponin A can be used clinically as the first choice for patients with long-term insomnia. In addition, date palm alkaloids are also effective in sedation and hypnosis, and Sun Yan et al. used date palm alkaloids in combination with saponins and found that the tranquilizing effect was significantly enhanced by the combination, and speculated that the mechanism of its antidepressant and the tranquilizing effect was related to the increase of 5-HT and NE content [24].

### 3.3. Inhibition of inflammation

There is some evidence that cytokines involved in immune function (CK) are associated with insomnia with anxiety and depression, and there is impaired immune function [25], where increased levels of inflammatory factors are accompanied by an inverse decrease in levels of anti-inflammatory factors, allowing impaired neuronal function and impeded neurotransmitter transmission. At the same time, excessive production of pro-inflammatory factors due to insomnia decreases the synthesis of 5-HT [26]. The organism, in the condition of inflammatory lesions of the nervous system, produces a stress response, and the activation of pro-inflammatory cytokines, glial cells, etc. can have a greater impact on the patient's mood, thus accelerating the onset of depression.

It has been found that the glutamatergic system can be hampered by a decrease in interleukin-6 (IL-6) and tumor necrosis factor (TNF- $\alpha$ ), which can even suppress the negative feedback effects of the HPA axis [27]. It has been suggested that significant increases in inflammatory markers such as serum C-reactive protein (CRP), IL-6, and TNF- $\alpha$  are seen in patients with depression [28,29]. Qin Meiyang et al. found that sour date soup could reduce IL-1 $\beta$ , CRP, and TNF- $\alpha$  levels, increase BDNF and GDNF levels, significantly inhibit inflammatory factors, increase neurotrophic factor levels, restore neurological function, and improve sleep quality in patients [30].

## 4. Summary and Outlook

In summary, the efficacy of sour date palm in the treatment of insomnia and anxiety, and depression is very positive and it is one of the most commonly used drugs in clinical practice, and its participation in the preparation of sour date palm soup is also the core prescription for the treatment of insomnia with anxiety and depression. In this paper, we conclude that sour date palm mainly regulates the function of the hypothalamic-pituitary-adrenal (HPA) axis, regulates neurotransmitters, inhibits inflammation, anti-anxiety, anti-depression, and protects brain nerves to achieve multi-target and multi-path treatment of insomnia with anxiety and depression.

Although sour date kernel has been widely used in clinical practice for the treatment of insomnia anxiety and depression, the pharmacological mechanisms of action of some of its active ingredients have been studied in a small number of studies. However, on the one hand, the research on the treatment of insomnia with anxiety and depression by sour date kernel is mostly in animal experiments and action pathways, and there is a relative lack of relevant clinical trials; on the other hand, the research on the active ingredients of sour date kernel is mostly in flavonoids and saponins, and the rest of the ingredients such as alkaloids, phenolic compounds, and amino acids are rarely studied. In addition, the correlation between the active ingredients of sour date palm and its preparation method and drug use content is not clear. Therefore, other active ingredients of sour date kernel and their pharmacological mechanisms should be further explored in the future; and more clinical studies should be conducted to investigate whether the dosage of addictive western drugs such as diazepam can be reduced. And to provide a theoretical basis for the clinical application of sour date kernel in the treatment of insomnia with anxiety and depression, so that it can be more widely used in clinical treatment.

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